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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/478,621	01/05/00	EPSTEIN S	674522-2001

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EXAMINER	
JIANG,D	
ART UNIT	**PAPER NUMBER**
1646	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/478,621	Applicant(s) EPSTEIN ET AL.	
	Examiner Dong Jiang	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *2,6 and 7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5 and 8-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4 and 5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED OFFICE ACTION

Applicant's election with traverse of Group I invention, claims 1, 3-5, and 8-11, in Paper No. 8, filed on 01 June 2001 is acknowledged. The traversal is on the ground(s) that claims in both Groups I and II are related to each other, in that the DNA in Group II encodes the protein of Group I, and there has been no showing of any undue or serious burden in searching and examining both DNA and the protein encoded thereby. Further, the applicant asserts that the overlapping of claims 8-10 between Groups I and II also evidence unity between the two groups. Applicants arguments are not found persuasive for the following reasons. First, as set forth in the previous office action, although the DNA molecules and proteins are related since the DNA encodes the specifically claimed protein, they are distinct compositions because they are *physically and functionally different*, and have *different properties and uses*. For example, the DNA can be used for the recombination production of the protein, gene therapy, and in hybridization assay, whereas the protein can be used for the production of antibodies, and screening for drugs. As any search of the prior art in regard to group I will reveal whether any prior art exists as to the Group II, a search is directed to references which would render the invention obvious, as well as references directed to anticipation of the invention, and therefore requires a search of relevant literature in different areas of subject matter. Additionally, the methods of the inventions are different because they utilize patentably distinct active agents, and the search for gene therapy will not overlapping with the search for administration of proteins. Further, the overlapping of claims 8-10 between the two Groups is due to the ways of the claims are composed. For instance, the independent claim 1 does not clearly define the effective ingredient of the composition as a protein or a DNA, indicating the possibility of either one. Therefore, the dependent method claims, such as claims 8-10, without further specifying the composition, read on either protein or DNA, which is the reason leading to the overlapping of claims 8-10 between the two Groups. Such ways of composing claims can not be used as an indication that the inventions in the two groups are not distinct.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 1, 3-5, and 8-11 are under consideration.

Formal Matters:

The disclosure is objected to because of the following informalities:

Claims 1, and 8-11 are objected to for encompassing a non-elected invention, a composition of a gene expression system, and the method of using such. Correction is required.

Claim 10 is objected to for missing the term "inducer" after "the vessel maturation".

Appropriate correction is required.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-5, and 8-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite for reciting "therapy for restenosis". It is unclear whether the therapy is to reduce or to increase the restenosis.

Claims 1 and 9 are indefinite for using parentheses, such as "(vessel maturation inducer)". It is unclear whether "vessel maturation inducer" in the parentheses is a part of the limitations of the claims, and if so, what limitation is imported by such.

Claim 9 is further indefinite because a kit usually *contains*, rather than *comprises* a polypeptide; to say that the kit comprises the polypeptide is to suggest that the polypeptide makes up a portion of the components that form the container itself. Additionally, it is unclear what is the interrelationship between the parts of the kit. As required, the interrelationships between the elements must be explicitly stated (see In re Venezia, 530 USPQ 2d 956 (CCPA 1975)).

The term "vessel maturation inducer" in claims 1, 4, 5, 9, and 10 is used by the claim to mean "an agent for inducing vessel maturation". However, it is not a recognized term in the art. Therefore, it is unclear what is meant by "vessel maturation inducer" in these claims, and what agents are encompassed by this term.

Claims 4 and 5 are further indefinite for failing to adequately and specifically identify the protein, "ang-1", from which the subject matter of the current invention was derived. In view of the prior art, the term "ang" has been applied to indicate different subject matters including different protein substances such as angiotensin. It is, therefore, necessary that the applicant clearly defines the term "ang" by sufficient identifying characteristics so as to clearly and distinctly indicate the protein that is the subject of the invention.

Claim 3 recites the limitation "the soluble VEGF receptor". There is insufficient antecedent basis for this limitation in the claim. The claim is further indefinite for using the term "comprising". The open language "comprising" indicates more than one agent in the VEGF inhibitor, but the fact is that only *one* agent, the soluble VEGF receptor, is used. "Wherein the VEGF inhibitor *is* the soluble VEGF receptor" is suggested.

The remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1, and the dependent claims 3, 4, and 8-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to a composition comprising the soluble VEGF receptor and angiopoeitin-1 (ang-1), does not reasonably provide enablement commensurate in scope with claims to a composition comprising a VEGF inhibitor and a vessel maturation inducer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claims 1, 3, 4, and 8-11 are directed to a composition comprising a VEGF inhibitor and a vessel maturation inducer, which, given the broadest interpretation, reads on any or all functional equivalents to inhibit VEGF or induce vessel maturation. For example, a VEGF inhibitor can be a soluble VEGF receptor, an anti-VEGF antibody, an anti-VEGF receptor antibody, antisense VEGF cDNA, low molecular weight inhibitors, etc. Enablement is not commensurate in scope with claims to any or all possible functional equivalents. The specification merely discloses *one* agent for inhibiting VEGF, the soluble VEGF receptor, and one agent for inducing vessel maturation, ang-1. The specification provides neither additional guidance nor working example other than the soluble VEGF receptor and ang-1, to teach how to make or use a commensurate number of VEGF inhibitor or vessel maturation inducer. It is not predictable that a random combination of any VEGF inhibitor with any vessel maturation inducer would produce the same functional effect as claimed. A skilled artisan would not be able to reasonably expect, for example, that administration of a VEGF inhibitor in combination with any "vessel maturation inducer" which does not activate Tie2 receptor (as ang-1 does), would induce the same effect as the composition of the soluble VEGF receptor and ang-1 does. The Office therefore concludes that the one of each agent is not representative of all VEGF inhibitors or vessel maturation inducers recited in claims 1, 3, 4, and 8-11.

It would require undue experimentation to find other agents having the desired activity, and then determine if such were suited to be used as disclosed. Due to the large quantity of experimentation necessary to determine how to make a commensurate number of VEGF inhibitor or vessel maturation inducer, such that it can be determined how to use the claimed agents or compositions, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, and the breadth of the claims which embrace a broad class of substances with no structural similarity, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim 8 and 9 are further not enabled for the limitation of "preventing" atherosclerosis or restenosis. In searching the prior art, the results of record have not established that atherosclerosis or restenosis can be prevented. All that has been shown is that these conditions can be treated. Prevention would necessarily mean that an individual would be given said

composition, and such administration would ensure that the patient did not develop atherosclerosis or restenosis. As there is no decisive means to predict who would be developing the conditions without the treatment, and such preventative effect has not been shown, the asserted utility of *preventing* the diseases is not enabled.

Rejections Over Prior Art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-5, and 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Inoue et al. (Circulation, Nov. 1998, 98(20): 2108-16), and Maisonpierre et al. (Science, July 1997, 277:55-60), in view of Kendall et al. (US 5,712,380), and Asahara et al. (Circ. Res., 1998, 83: 233-240).

Inoue demonstrates the expression of VEGF and its receptors in the progression of human coronary atherosclerosis, and distinct expression of VEGF mRNA in human coronary atherosclerotic plaques, but not in normal coronary arteries (Figures 1-5, and page 2113, the first and the second paragraph of the Discussion), and suggests that VEGF is capable of inducing neointimal angiogenesis and intimal hyperplasia, and may promote process of atherosclerosis (the last sentence of the abstract, and the last paragraph of the reference). Additionally, Inoue

teaches that the coronary occlusive lesions have extensive neovascularization, and intense immunostaining for VEGF was observed in accumulated macrophages and endothelial cells of the microvessles (the second paragraph of the abstract).

Maisonpierre discloses that angiopoietin-2 (ang-2) is a natural antagonist for ang-1 and the Tie2 receptor, and is expressed only at sites of vascular remodeling (the abstract). Additionally, Maisonpierre teaches that angiopoietins and Tie2 do not participate in the initial vasculogenic phase of vascular development, but rather play critical roles in angiogenic outgrowth, vessel remodeling, and maturation (page 59, the left column, the first sentence of the last paragraph), and that ang-1 may provide a maturation or stabilization signal through Tie2 that can be blocked by ang-2, such inhibition may result in continued remodeling or the initiation of vascular sprouting in the context of simultaneous VEGF exposure (page 59, the left column, the 8th line from the bottom). Further, Maisonpierre teaches that therapeutic manipulation of vessel growth, - either positively or negatively, - is likely to require simultaneous regulation of both the VEGF and angiopoietin systems (page 59, the middle column, lines 1-5).

Kendall teaches a soluble VEGF receptor, and indicates that it would be useful as a treatment for persistent pathological angiogenesis (column 1, lines39-45).

Asahara teaches applications of VEGF, angl, or ang2 in the study of neovascularization in vivo, and demonstrates that neither angl nor ang2 alone promoted neovascularization (line 7 of the abstract), and that ang2 + VEGF promoted significantly longer and more circumferential neovascularity, whereas angl + VEGF does not affect the length or circumferential neovascularity (lines 9-12 of the abstract).

None of the references teaches to make a composition comprising a VEGF inhibitor, such as a soluble VEGF receptor, and an angiopoietin, such as ang-1, and to use it to treat atherosclerosis/restenosis.

With respect to claims 1, and 3-5, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to make a composition comprising a VEGF inhibitor, such as a soluble VEGF receptor, and ang-1, and to use it to treat atherosclerosis/ restenosis because of teachings by Inoue and Maisonpierre: that occlusive atherosclerosis lesions have extensive neovascularization, and intense VEGF expression, suggesting that VEGF promotes process of atherosclerosis (Inoue's teaching), which provides strong logical indication to apply a

VEGF inhibitor for the condition; and that ang-2, an antagonist of ang-1, promotes continued remodeling or the initiation of vascular sprouting in the context of simultaneous VEGF exposure, and therapeutic manipulation of vessel growth is likely to require simultaneous regulation of both the VEGF and angiopoietin systems (Maisonpierre' teaching), which suggests a combination therapy of a VEGF inhibitor and ang-1.

The person of ordinary skill in the art would have been motivated to make the composition in order to treat atherosclerosis/restenosis, and reasonably would have expected success because of the teachings of Kendall and Asahara, which indicate that both ang-2 and VEGF are required for neovascularization, which would immediately suggest to the artisan that inhibiting both would effectively prevent neovascularization also known as restenosis.

With respect to claims 8-11, none of the references teach a kit containing said composition. However, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to make a kit containing said composition, because such kit would facilitate its commercial distribution, and clinical practice. Packing of useful drugs in kits is old and well known in the art.

Conclusion:

No claim is allowed.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 703-305-1345. The examiner can normally be reached on Monday - Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER

DJ
7/11/01